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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,325	07/12/2004	Andreas Finke	RDID01062CUS	8527
49437	7590	05/02/2007	EXAMINER	
BARNES & THORNBURG LLP 11 SOUTH MERIDIAN STREET INDIANAPOLIS, IN 46204				FOSTER, CHRISTINE E
ART UNIT		PAPER NUMBER		
		1641		
MAIL DATE		DELIVERY MODE		
		05/02/2007		
		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/774,325	FINKE ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 23 February 2007.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-3,5,9,11-13 and 15-20 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-3,5,9,11-13 and 15-20 is/are rejected.
- 7) Claim(s) 13 is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)	5) <input type="checkbox"/> Notice of Informal Patent Application
Paper No(s)/Mail Date _____	6) <input type="checkbox"/> Other: _____

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/23/07 has been entered.
2. Claims 10 and 14 were canceled. New claim 20 has been added. Claims 1-2, 11-12, 15-17, and 19 were amended. Claims 1-3, 5, 9, 11-13, and 15-20 are currently pending and under examination.

### ***Manner Of Making Amendments Under 37 CFR 1.121***

3. Applicant is reminded of the proper format for amendments to the claims. In the interest of expediting prosecution, Applicant's amendment of 2/23/07 has been accepted. However, it is noted for the record that the amendments to claims 1, 9, 15, and 19 are non-compliant for the following reasons:
4. All claims being currently amended must be presented with markings to indicate the changes that have been made relative to the immediate prior version. The amendments to claim 1 are non-compliant because the immediate prior version of the claim (see the claim listing of 10/4/06) recited step (b) as follows:

(b) coating the protein onto the microparticles by adsorption under strongly alkaline conditions, wherein the pH of said combination is between 10.5 and 12.5, and

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The current version of the claim in the amendment of 2/23/07 recites:

(b) coating the protein onto the microparticles by adsorption under strongly alkaline conditions, wherein said coating step is conducted for a period of 1 to 10 days at a pH of said combination has a value selected from a range of about 10.5 to about 12.5, and

The amendments are non-compliant because the words “**has a value**” were not previously recited in the prior version of the claim, and should therefore not appear with strike-through marks in the current version of the claim. The currently presented claim would suggest that this text was deleted relative to the prior version, when in fact it was not present in the prior version. Furthermore, the words “**selected from a range of about 10.5 to about 12.5**” did not appear in the prior version of the claim, yet they are not presented in the current version with appropriate markings to indicate that they have been inserted. In addition, the words “**is between**” have apparently been deleted from the claim, yet there are no markings to indicate such a change.

5. Claim 9 is presented with the status identifier “Previously Presented”, which is incorrect because it is apparent that the claim has been currently amended, since the claim text presented is substantially different than given for the claim in the immediate prior version of the claim. The amendments are also non-compliant because there are no markings to indicate the changes that have been made relative to the prior version of the claim. The claim previously recited:

9. (new) The method of claim 1 wherein the protein has a size of 20 nm to 250 nm.

The amendment of 2/23/07 presents the text for claim 9 as follows:

9. (Previously Presented) The method of claim 5 wherein the microparticles have a size of about 2.5  $\mu\text{m}$  and consist essentially of about 88% polystyrene and 12% magnetite.

6. The amendments to claim 15 are non-compliant because the immediate prior version of the claim (10/4/06) recited in lines 6-7:

...the pH of said suspension between 10.0 and 12.5,...

The amendment of 2/23/07 presents the text as follows:

... the pH of said ~~suspension combination is selected from the range of about~~ ~~between~~ 10.0 to about 12.5;...

It can be seen that the words “**to about**” have apparently been inserted before the number “12.5”; however, there are no markings to indicate this change. In addition, the word “**and**” has apparently been deleted between the numbers “10.0” and “12.5”, yet there are no markings to indicate such a change. Furthermore, the comma that appeared after the number “12.5” has apparently been replaced with a semicolon, yet there are no markings to indicate such a change.

7. The amendments to claim 19 are non-compliant because the immediate prior version of the claim recited in lines 1-2:

...a pH value between 10.0 and 12.5...

However, the instant amendments recite:

~~...a pH value selected from the range of about 10.0 to about 12.5...~~

This is improper because the words “**selected from the range of about 10.0 to about 12.5**” did not appear in the prior version of the claim, and therefore should not be indicated as having been deleted through the use of strike-through marks in the current version of the claim. In addition, the words “**between**” and “**and**” in the phrase “between 10.0 and 12.5” have apparently been deleted from the claim, yet there are no markings to indicate such changes.

See 37 CFR 1.121 and MPEP 714.

***Objections/Rejections Withdrawn***

8. The objections to claims 16-17 and 19 as failing to further limit have been withdrawn in response to the amendments to claim 15 to recite a method “comprising” rather than a method “consisting of”.
9. The objections to claims 12 and 15 have been obviated by the amendments.
10. The rejection of claim 1 under 35 USC 112, 1<sup>st</sup> paragraph as containing new matter for recitation of the pH range of **10.5 to 12.5** (see the previous Office action at pages 4-5, item 12) has been withdrawn in response to Applicant’s amendments to incorporate the limitations of claim 10 (now canceled) into the independent claim.
11. The rejections of claims 14 and 19 under 35 USC 112, 1<sup>st</sup> paragraph as containing new matter in regard to recited steps of adjusting the pH (see the previous Office action at pages 5-6, item 13) have been withdrawn in response to the amendments to claim 19 and in light of the cancellation of claim 14.
12. The rejection of claim 2 under 35 USC 112, 1<sup>st</sup> paragraph as containing new matter in regard to the recitation of protein polymerized by chemical treatment has been withdrawn in response to Applicant’s amendments.
13. The rejections of claims 1 and 15 under 35 USC 112, 2<sup>nd</sup> paragraph for recitation of the relative term “strongly” in relation to alkaline conditions have been obviated by the amendments.
14. The rejections of claims 15 and 17 under 35 U.S.C. 102(b) as being anticipated by Vaynberg et al., and of claims 16 and 18-19 under 35 USC 103(a) as being unpatentable over Vaynberg et al., have been withdrawn in light of the amendments to claim 15 to recite an incubation time of 1-10 days; Vaynberg et al. teach an incubation time of 8-10 hours.

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15. The rejections of claims 1-2 and 13 under 35 U.S.C. 102(b) as being anticipated by Lou et al. (US 4,329,151), and of claims 5, 10-12, and 14 under 35 USC 103(a) as being unpatentable over Lou et al., have been withdrawn in response to the amendments to claim 1 to recite a method “consisting of” the recited steps, elements, and ingredients, to the exclusion of any unspecified steps, elements or ingredients.

16. The rejections of claims 15 and 17 under 35 U.S.C. 102(b) as being anticipated by Lou et al., and of claims 16 and 18-19 under 35 USC 103(a) as being unpatentable over Lou et al. in view of various references, have been withdrawn in light of the amendments to claim 15 to recite that the incubation is performed “in the absence of a crosslinking agent”. However, it is noted that the art rejection may be re-applied should the claims be amended to address the new matter rejection under 112, 1<sup>st</sup> paragraph set forth below.

17. The rejections of claims 1-3, 5, and 9-14 under 35 USC 103(a) as being unpatentable over Vaynberg et al. are withdrawn in response to the amendments to claim 1 to recite a method “consisting of” the recited steps, elements, and ingredients, to the exclusion of any unspecified steps, elements or ingredients, and in light of the cancellation of claim 10.

18. Claims 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmid in view of Vaynberg et al., Lou et al., and Serra et al. is withdrawn in favor of the rejection over Schmid in view of Vaynberg et al., Lou et al., and Amiral et al. set forth below.

*Specification*

19. The amendment filed 10/6/2005 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall

introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment of 10/6/2005 inserts an **incorporation by reference statement** in the benefit claim in the first paragraph of the specification. The statement “The content of both prior-filed applications are incorporated herein by reference” includes the foreign priority application, EP 01118812.5, filed on August 10, 2001, which was not previously incorporated by reference as required by CFR 1.57(b).

MPEP § 608.01(p) states that incorporation by reference that was not incorporated by reference on filing of an application may introduce new matter. Therefore the added statement as set forth above introduces new matter into the disclosure of the invention. An incorporation by reference statement added after an application's filing date is not effective because no new matter can be added to an application after its filing date (see **35 U.S.C. 132(a)**). When a benefit claim under **35 U.S.C. 120** is submitted after the filing of an application, the reference to the prior application cannot include an incorporation by reference statement of the prior application. MPEP 201.06(c). See *Dart Indus. v. Banner*, 636 F.2d 684, 207 USPQ 273 (C.A.D.C. 1980).

Applicant is required to cancel the new matter in the reply to this Office Action.

### ***Claim Objections***

20. Claim 13 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

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21. Claim 13 depends from claim 1, which has been currently amended to recite a method “**consisting of** the steps of” (a)-(c) that follow (emphasis added). Applicant has intentionally employed the closed transitional phrase “**consisting of**” to limit the scope of the claim to the specified steps that follow and to *exclude any element, step, or ingredient not specified in the claim* (see Reply, page 9). See also the previous Office action at page 3, item 7; and MPEP 2111.03.

However, claim 13 recites a method “wherein said coating step is conducted with a buffer...”. The dependent claim fails to further limit the parent claim since it recites an additional element or ingredient not specified in the parent claim, namely a buffer. As such, the dependent claim does not properly depend from the parent claim since it includes additional ingredients or elements that are not specified in the parent claim, yet the scope of the parent claim is closed, such that additional ingredients have been specifically excluded.

For the purposes of examination, claim 13 was interpreted as being drawn to a method according to claim 1, wherein the recited buffer is also employed. However, the scope of the claim has been otherwise construed as excluding any element, step, or ingredient not specified in the claim, in light of Applicant’s explicit use of the closed transitional language “consisting of” in claim 1.

22. Claim 15 is objected to because the preamble of the claim recites a method for producing protein-coated *polystyrene* microparticles; however, the body of the claim refers only to “microparticles”. It is suggested that at the first reference to “microparticles” in the body of the claim (step (a)) that the adjective “*polystyrene*” also be included in order to maintain consistency with the claim preamble.

***Claim Rejections - 35 USC § 112***

23. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

24. Claims 1-3, 5, 9, 11-13, and 15-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.*

25. The instant amendments to claims 1 and 15 introduce new matter in that claim 1 now recites that the coating step is conducted “at a pH **selected from a range of about 10.5 to about 12.5**”. Similarly, claim 15 now recites that the pH is “**selected from the range of about 10.0 to about 12.5**”.

It is noted that prior versions of the claims did not include the term “about” in relation to the claimed pH ranges (see the claim set of 10/4/06 and the remarks above regarding the manner of making amendments under 37 CFR 1.121). The amendments of 2/23/07 to insert the term “about” in relation to the claimed pH ranges broadens the scope of the claims in a manner unsupported by the original disclosure.

Applicant’s reply states that new matter has not been introduced (see Reply, page 5), but did not specifically indicate where support for the amendments may be found. The examiner was

unable to find support in the specification and claims as originally filed for the claimed methods involving pH values of “**about 10.5 to about 12.5**” or “**about 10.0 to about 12.5**”.

Although the specification discloses that coating is preferably carried out at a pH “**between pH 10.0 and pH 12.5**” (see [0015]), there is no written description of the claimed ranges of “**about 10.0 to about pH 12.5**” and “**about 10.5 to about 12.5**”.

The insertion of the term “**about**” broadens the scope of the claims so as to include pH values of, for example, pH 13.5, which are described in the specification. Such broadening amendments, in going beyond the scope of the original disclosure, depart from the specification and claims as originally filed.

26. Claim 15 as currently amended recites step (d) in which the combination is incubated “**in the absence of a crosslinking agent**” Applicant’s reply states that new matter has not been introduced (see Reply, page 5) and indicates that support may be found for the amendment in original claim 1 and in paragraphs 15, 25, and 30 (see Reply, page 8).

The stipulation that the method be carried out “in the absence of a crosslinking agent” represents a negative limitation that is not supported by the original disclosure. MPEP 2173.05(i) states:

Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) (“[the] specification, having described the whole, necessarily described the part remaining.”). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), aff’d mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

In the instant case, the specification fails to include a positive recitation wherein the claimed methods are performed in the presence of a “crosslinking agent”. The term “crosslinking agent” was not found in the specification. Because the element of a “crosslinking agent” is not positively disclosed in the specification, its explicit exclusion in the claims lacks basis in the original disclosure and therefore represents new matter.

27. Claim 15 recites that the protein “has a size from 10 nm to 300 nm”. The specification discloses protein material having “a size of at least 10 nm up to a maximum of 300 nm determined by photon correlation spectroscopy” [0025]. However, it is noted that claim 15 does not recite photon correlation spectroscopy in relation to the size of the protein. The incorporation of the size limitation of “10 nm to 300 nm” without the accompanying disclosed limitation of “determined by photon correlation spectroscopy” represents new matter because it broadens the scope of the claim so as to include proteins having a size of 10-300 nm as determined by any method of measurement.

Applicant has previously argued (see the Reply of 10/4/2006 at pages 12-13) that the limitation of “photon correlation spectroscopy” is significant and should be given weight, arguing that the actual size of a protein can differ by several mechanisms, such that “any comparison of protein size should be made as taught in applicants specification, namely photon correlation spectroscopy”. In light of Applicant’s arguments that there is a distinction between proteins having a size of 10-300 nm *as determined by photon correlation spectroscopy* and proteins having a size of 10-300 nm as determined by other methods, one skilled in the art would

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not envisage possession of methods involving all proteins of size 10-300 nm (as determined by any method) based on the disclosure of proteins of size 10-300 nm *as determined by photon correlation spectroscopy.*

28. Claims 13 and 17 recite that the coating step is conducted with a buffer “having a salt content of **about 0.3 to about 1.5 M**”. The specification discloses at [0031] that:

The coating is preferably carried out with a buffer which has a salt content of 0.1 to 2 M, particularly preferably 0.3 to 1.5 M and especially preferably of 0.8 to 1.2 M.

The specification does not fully support the claimed subject matter because the range “**about 0.3 to about 1.5 M**” is broader in scope than the disclosure of “**0.3 to 1.5 M**”.

29. Claims 9 and 18 recite that “the microparticles have a size of about 2.8  $\mu\text{m}$  and **consist essentially of about 88% polystyrene and 12% magnetite**”. The specification discloses at [0022] that:

DYNABEADS from the DYNAL Company having a size of ca 2.8  $\mu\text{m}$  and consisting of 88% polystyrene and 12% magnetite such as the hydrophobic beads M-280 or the epoxy beads M-270 are, for example, suitable.

The new claim represents new matter because (1) the transitional phrase “**consisting essentially of**” defines a *different scope* than “**consisting of**” as disclosed in the specification (see MPEP 2111.03). Further, the claimed “**about 88%**” is broader in scope than the disclosed “88%”, since the insertion of the term “about” broadens the scope of the claim to include, for example, particles having 87% or 89% polystyrene. There is no description of uncoated polystyrene microparticles “**consisting essentially of about 88% polystyrene and 12% magnetite**”.

In addition, the examples of M-270 and M-280 as in the above passage would seem to be directed to **coated** rather than **uncoated** microparticles. See the specification at paragraph 3, and also Hornes et al. (US 5,512,439), columns 3-4, and especially at column 4, lines 25-31, which describes the functionalized coatings of hydroxyl groups on M-280 DYNABEADS. Thus there appears to be no disclosure of **uncoated** microparticles having the recited composition.

Applicant's clarification is requested.

Additionally, the passage above discloses the claimed size and composition only in describing the properties of "**DYNABEADS**". This description of DYNABEADS having the recited size and composition does not fully support the claim, which now encompasses **all microparticles** with a size of about 2.8  $\mu\text{m}$  that consist essentially of about 88% polystyrene and 12% magnetite.

30. Claim 16 recites that the length of the incubation step is "about 4 to about 7 days". The specification discloses the range of "4 – 7 days" at [0030], [0046]. However, there is no disclosure of the range of "about" 4 to "about" 7 days as currently claimed. As noted above, the insertion of the term "**about**" broadens the scope of the claim, in a manner unsupported by the original disclosure.

31. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

32. Claim 1-3, 5, 9, and 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

33. Claim 1 is indefinite because it recites the broad recitation "**alkaline conditions**" together in the same claim with "**a pH selected from a range of about 10.5 and about 12.5**", which is a narrower statement of the range/limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

If Applicant intends the term "alkaline conditions" simply as a means of characterizing or describing the recited pH range of 10.5-12.5, it is suggested that the term instead be employed in the preamble.

34. Claim 20 recites the limitation "said coating step". There is insufficient antecedent basis in the claims for this limitation.

***Claim Rejections - 35 USC § 102***

35. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

36. Claim 15 is rejected under 35 U.S.C. 102b) as being anticipated by Kakabakos et al. (“Immobilization of Immunoglobulins onto Surface-Treated and Untreated Polystyrene Beads for Radioimmunoassays” *Clin. Chem.* 36 (1990), 492-496 in light of Song et al. (“Effects of Cosolvents and pH on Protein Adsorption on Polystyrene Latex: A Dynamic Light Scattering Study” *Journal of Colloid and Interface Science* 221 (2000), 25-37).

Kakabakos et al. teach a method for producing protein-coated polystyrene microparticles (beads), in which a suspension of uncoated polystyrene microparticles (in water) is added to a protein (IgG) to form a combination of pH 9.6 (which is in the range of “about” 10.0). See in particular the abstract and p. 492, left column; p. 492, right column, the first paragraph; and p. 493, left column, the sections “Polystyrene beads and surface treatment” and “Solid-phase immobilization protocol”; and Figures 1 and 3. It is noted that antibodies are specifically mentioned as examples of bioaffinity binding pairs in the specification at [0025]. As such, the IgG antibody taught by Kakabakos et al. meets the limitation of being a partner of a bioaffinity binding pair.

The IgG is incubated with the microparticles for 24-48 hours in the absence of a crosslinking agent (p. 493, left column, “Solid-phase immobilization protocol”; the paragraph bridging pages 493-494; and Figure 2). Coating of the microparticles is by adsorption (see

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especially the abstract). The reference further teaches separating non-adsorbed protein from protein-coated microparticles by washing (p. 493, left column, “Solid-phase immobilization protocol”).

Kakobakos et al. do not mention that the IgG has a size from 10 nm to 300 nm.

Song et al. is relied upon as an evidentiary reference to show that IgG meets the claimed size limitation. Song et al. measured the size of this protein by photon correlation spectroscopy (“dynamic light scattering”), which is the method disclosed in the instant specification [0025]. The reference provides evidence that IgG has a size within the range of 10-300 nm, since for all measurements performed, the hydrodynamic diameter of IgG was within this claimed range (see page 27, “DLS experiments”; Table 3; and page 30 in particular).

Therefore, in light of the evidence of Song et al., the protein of Kakobakos et al. meets the limitation of being a protein of size 10-300 nm.

### ***Claim Rejections - 35 USC § 103***

37. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

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2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

38. Claims 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmid (DE 199 24 643 A1, Applicant's Information Disclosure statement of 5/6/04) in view of Vaynberg et al. ("Polyampholyte Gelatin Adsorption to Colloidal Latex: pH and Electrolyte Effects on Acrylic and Polystyrene Latices," *Biomacromolecules* 1 (2000), 466-472), Amiral et al. (US 5,175,112), and Lou et al. (US 4,329,151). The references are of record.

Although a translation of the Schmid reference (which is in German) was not submitted by Applicant, this rejection is being made pursuant to a consultation between the examiner and STIC translator J.M. Koytcheff on 11/13/2006.

Schmid teaches methods of coating microparticles with proteins by adsorption (column 1, lines 25-68). Specifically, Schmid teaches a method where microparticles are contacted with a protein in suspension, subjected to uniform heating for 10-90 minutes, maintained at the elevated temperature for 0-50 hours, and then irradiated with UV light (see the entire document, especially column 1, lines 1-11; column 3, lines 1-21; column 4, lines 5-43; the Example, and

claim 1). The reference teaches that this process results in microparticles with high binding capacity and reduced bleeding, and allows for large-scale production. Suitable particles include DYNABEADS of size 2.8 microns and having 88% polystyrene and 12% magnetite (column 2, lines 29-35). The proteins to be coated are preferably hydrophobic, and have a size that can vary from 20-300 nm; a preferred size is 50-200 nm since a size ratio between particles and protein is preferably from >10:1 with >20:1 being particularly preferred (column 2, lines 36-68). The reference teaches that polymerized proteins strengthen the absorption and have a larger number of binding sites. Polymerized streptavidin (poly-SA) is specifically mentioned as having high binding capacity and low bleeding tendency (column 2, lines 59-68). The process allows for protein-charged microparticles useful as a test phase in medicinal, immunological, and diagnostic assays.

Schmid does not mention a “crosslinking agent”, such that the reaction occurs in the absence of a crosslinking agent as claimed. It is noted that although the reference teaches the steps of heating and UV light irradiation, there is nothing in the instant specification to indicate that such steps would be considered “crosslinking agents” since this term is not disclosed or defined.

The reference differs from the claimed invention in that it fails to specifically teach that the coating pH is selected from a range of about 10 to about 12.5. In Schmid, a pH of 7.0 is exemplified (the example). With respect to the length of incubation, the reference also fails to specifically teach the claimed range of 1-10 days, but teaches a total incubation time of 10-90 minutes plus an additional 0-50 hours as noted above.

With respect to the limitation that the combination is incubated for 1-10 days, Schmid teaches that the microparticles and protein are subjected to uniform heating for 10-90 minutes and then maintained at the elevated temperature for 0-50 hours (column 2, lines 1-10, column 3, lines 1-21). Because the claimed ranges overlap the range of 10-90 minutes plus an additional 0-50 hours disclosed by Schmid, a *prima facie* case of obviousness exists. MPEP 2144.05. As such, and in the absence of evidence of criticality, it would have been obvious to conduct the method of Schmid at the recited incubation times given that the claimed ranges overlap those disclosed in the reference.

With respect to the reaction pH, it is known in the art that pH is a result-effective variable in the adsorption of proteins onto particles, as taught by Vaynberg et al., Amiral et al., and Lou et al. It was also known in the prior art to coat proteins onto polystyrene particles within the claimed pH range of about 10 to about 12.5.

Amiral et al. also teach that when adsorbing proteins onto latex particles (including polystyrene latex), experimental conditions including pH are adjusted according to the nature of the product to be assaying in order to ensure stability, maximum reactivity, reproducibility, and preservation (see especially column 9, lines 30-50; and column 7, lines 1-11 and 49-66). The reference notes in particular that increasing the pH results in *stabilization* of immunological reagents to be coated, and teaches adsorption at pH in the range of 4-10 (column 9, lines 50-61).

Vaynberg et al. teach that the properties of proteins adsorbed onto polystyrene microparticles can vary in response to pH (p. 467, left column, the second paragraph; p. 470-471, “Adsorption Isotherms”). In particular, increasing pH was found to be associated with a swelling of the hydrodynamic layer thickness, reflecting underlying changes in the structure of the

adsorbed protein layer (Figure 8, p. 470, right column, and p. 471, left column, the first full paragraph). Vaynberg et al. exemplify coating protein onto polystyrene microparticles at high pH values including pH 10 (see p. 469, left column; and Figures 2, 6, and 8 in particular; experiments were conducted over the range pH 5.7-10). The reference also teaches that measurements of the layer thickness and layer hydrodynamic radius (which were found to change as a function of pH) can be used to validate models of the adsorbed protein layer structure (page 472).

Lou et al. also teach that adsorption of proteins onto polystyrene particles is affected by pH, temperature, and other factors (column 4, lines 19-33). In particular, the reference teaches that pH can affect the stability of adsorbed proteins, and report that by adsorbing the protein streptolysin-O at high pH values of 8.5-11.9, the resulting product was more stable and the adsorbed protein substantially retained pre-adsorption characteristics (column 3, lines 34-38; column 4, lines 19-63; column 8, lines 53-59).

Therefore, it would have been obvious to one of ordinary skill in the art to conduct the method of Schmid within the recited pH range of 10.0-12.5 in the course of routine optimization, out of the normal desire of artisans to improve upon what is already known. In particular, it would have been obvious to optimize the pH and in particular to select pH values within the recited pH ranges, given that it was known in the art to coat proteins onto polystyrene microparticles at pH values up to and in excess of pH 10, as taught variously by Vaynberg et al., Amiral et al., and Lou et al. As such, it would have been obvious to optimize within the ranges taught in the prior art, which overlap the currently claimed ranges. In the case where the claimed

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ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. MPEP 2144.05.

It would have been obvious to do this since pH is recognized in the prior art as a result-effective variable in methods of adsorbing protein onto polystyrene particles, in that the pH of the coating reaction can affect the structure, stability, reactivity, reproducibility, and preservation, as taught by Amiral et al. Vaynberg et al., and Lou et al.

The Amiral et al. reference provides additional motivation for adsorbing at higher pH, teaching that increasing pH results in stabilization of the coated reagent. Lou et al. also teach that the stability of streptolysin-O protein-coated particles is increased at high alkaline pH (see especially column 4, lines 34-37). As such, it would have been obvious to conduct the method of Schmid at higher pH in order to increase the stability of the coated protein.

Vaynberg et al. teach that the structure of the adsorbed protein can change as a function of pH, and that measurements of the adsorbed protein layer can be used to generate structural models (see especially pages 470-471, "Adsorption Isotherms"; and p. 472). As such, it would have been obvious to increase the adsorption pH in order to generate structural models to study the structure of the protein as a function of pH.

Moreover, Vaynberg et al. teaches that adsorption of protein onto polystyrene is dominated by hydrophobic interactions, such that there is "little variation" in the level of adsorption over a broad range of pH values, including alkaline pH values of up to pH 10 (see the entire document, especially at p. 467-468, "Adsorption Isotherms"; p. 469-470). Amiral et al. also exemplify adsorption of proteins onto microparticles at pH values of 4-10. As such, one would have a *reasonable expectation of success* in optimizing the pH of the coating reaction in

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the method of Schmid as Vaynberg et al. teach that pH variations hardly affect adsorption levels on polystyrene. One would also have a reasonable expectation of success in light of the teachings of Vaynberg et al., Amiral et al., and Lou et al., which all teach adsorption of protein onto polystyrene at pH values up to and/or in excess of pH 10.

With respect to claims 16 and 20, Schmid teaches that this time is important for the effectiveness of the method (column 4, lines 5-25). Although Schmid et al. do not specifically teach a length of incubation that is 4-7 days as recited, the reference clearly teaches that incubation time is a result-effective variable impacting the effectiveness of the coating method. Amiral et al. also teach that the reaction time is an experimental condition that may be adjusted according to the nature of the product to be assayed in order to ensure stability, reactivity, and preservation (column 9, lines 30-45).

Therefore, in light of the fact that incubation time was known in the prior art to have effects on protein adsorption, and in the absence of evidence of criticality, it would have been obvious to one of ordinary skill in the art to optimize the incubation time out of the normal desire of artisans to improve upon what is already known.

With respect to claim 17, Schmid teaches 50 mM K<sub>2</sub>HPO<sub>4</sub> (the example). Ionic strength is recognized in the prior art as a result-effective variable in the adsorption reaction of proteins to polystyrene. For example, Amiral et al. teaches that increasing the ionic strength stabilizes adsorbed immunological reagents (column 9, lines 30-50). The reference exemplifies buffers of ionic strength in the range of 0.01-0.5M, which overlaps the claimed range of 0.3-1.5M (column 10, lines 4-21).

See also Lou et al., which also teaches that adsorption of proteins onto polystyrene particles is affected by ionic strength (column 4, lines 19-33).

Given that ionic strength is recognized in the prior art as a result-effective variable in the adsorption of proteins onto polystyrene, it would have been obvious to one of ordinary skill in the art to perform the method at the recited buffer concentration through routine optimization out of the normal desire of artisans to improve upon what is already known. In addition, in light of the teachings of Lou et al. and Amiral et al. that increased ionic strength increases the stability of the adsorbed protein, it would have been obvious to increase the buffer concentration over that exemplified by Schmid.

39. Claims 16-17 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kakabakos et al. (in light of Song) in view of Amiral et al.

Kakabakos et al. is as discussed above, which teaches incubation times of 1-2 days (24-48 hours). The reference fails to specifically teach incubation times of 4-7, or about 4-7, days as in claims 16 and 20. The reference also fails to specifically teach a buffer having a salt content of about 0.3 to about 1.5 M as in claim 17.

In the instant case, the prior art recognized incubation time as a result-effective variable in the adsorption of proteins onto microparticles, including polystyrene microparticles. For example, Amiral et al. (discussed above) teach that the duration of the reaction is one experimental condition that can be adjusted in order to ensure the stability, reactivity, and preservation of the product (column 9, lines 5-50). This is also taught in Kakabakos et al., in that

the immobilization of IgG onto the polystyrene beads increased as a function of time (see Figure 2 and the paragraph bridging pages 493-494).

Absent a showing that the particular claimed range of 4-7 days is critical, it would have been obvious to one of ordinary skill in the art to optimize the length of the incubation out of the normal desire of artisans to improve upon what is already known. In particular, it would have been obvious to increase the incubation time in order to achieve increased adsorption of protein onto the beads, given that increasing incubation time was known to have the effect of increasing the amount of protein immobilized. See MPEP § 716.02 - § 716.02(g) for a discussion of criticality and unexpected results.

With respect to claim 17, ionic strength is also recognized in the prior art as a result-effective variable in the process of protein adsorption to solid surfaces, including polystyrene particles.

For example, Amiral et al. teaches that ionic strength is one experimental condition that is adjusted according to the nature of the product to be assayed when adsorbing proteins onto latex particles, in order to ensure the stability, reactivity, and preservation of the product. In particular, the reference teaches that increasing the ionic strength stabilizes adsorbed immunological reagents (column 9, lines 30-50). The reference exemplifies buffers of ionic strength 0.01-0.5M, which overlaps the claimed range of 0.3-1.5M (column 10, lines 4-21).

Absent a showing that the particular claimed range of 0.3 to 1.5M is critical, it would have been obvious to one of ordinary skill in the art to optimize the ionic strength out of the normal desire of artisans to improve upon what is already known, given that it was known in the prior art to conduct adsorption reactions at ionic strengths overlapping the claimed ranges.

In particular, it would have been obvious to increase the ionic strength in order to increase the stability of the adsorbed protein, as taught by Amiral et al.

40. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kakabakos et al. (in light of Song) in view of Amiral et al. as applied to claim 17 above, and further in view of Bangs (“New developments in particle-based immunoassays: introduction” (1996) *Pure & Appl. Chem.* **10**:1873-1879) and Gudiband et al. (US 5,686,244).

Kakabakos et al. and Amiral et al. are as discussed above. Kakabakos et al. teaches polystyrene microparticles, but fails to specifically teach that the particles have a size of about 2.8 microns and consist essentially of about 88% polystyrene and 12% magnetite.

Bangs et al. teach superparamagnetic particles, which can be used in radioimmunoassay, ELISA's, and other assays in order to help pull things out of solution more quickly (page 1876). In particular, magnetic particles allow for fast and easy separation of solid and liquid phases.

Gudiband et al. teach the superparamagnetic DYNAL M-280 Dynabeads, which have a 2.8 micron diameter (column 21, Example VII). These are the same beads disclosed in the instant application as consisting of 88% polystyrene and 12% magnetite [0022]; thus, the beads meet the recited limitations as to the composition. Thus, superparamagnetic particles of the recited size and composition were known in the prior art.

Therefore, it would have been obvious to conduct the method of Kakabakos et al. and Amiral et al. using the M280 microparticles taught by Gudiband et al., rather than the polystyrene beads taught by Kakabakos et al. One would be motivated to use the microparticles of Gudiband et al. because they are superparamagnetic, which permits fast and easy separation of

the solid and liquid phase in radioimmunoassays (as taught by Bangs); which is the intended use of the coated particles of Kakabakos et al. (see the title).

It would have been obvious to select the known M280 particles based on its art-recognized suitability for its intended use, in that Gudiband et al. teaches that the particles are superparamagnetic. See MPEP 2144.07. One would have a reasonable expectation of success because Gudiband et al. teach that the particles are capable of being coated with protein for use in specific binding assays.

#### *Response to Arguments*

41. Applicant's arguments filed 2/23/07 have been fully considered.
42. With respect to the rejections of claims 17-18 under 35 USC 112, 1<sup>st</sup> paragraph as containing new matter (see the instant rejections of claims 9, 13, and 17-18 above), Applicant's arguments (see pages 6-7) have been fully considered but they are not persuasive.

With respect to claims 13 and 17, at issue is whether the disclosed range of “0.3 to 1.5 M” provides written description for the claimed range of “**about** 0.3 to **about** 1.5 M”.

With respect to claims 9 and 18, at issue is whether the disclosure of “DYNABEADS from the DYNAL Company having a size of ca 2.8  $\mu\text{m}$  and **consisting of** 88% polystyrene and 12% magnetite” adequately supports the instant claims involving all microparticles having a size of about 2.8  $\mu\text{m}$  and **consisting essentially of** 88% polystyrene and 12% magnetite.

Applicant first argues (see page 7, first paragraph) that there is no *in haec verba* support requirement for complying with 35 USC 112, 1<sup>st</sup> paragraph, which is not on point because the

rejection does not contend that the claims lack only for literal support in the specification. As such, the argument is not persuasive because it does not actually address the rejection.

Applicant further argues (see page 7, the second full paragraph) that the amendments do not “substantially” increase the scope of the claims. It appears that Applicant acknowledges that the specification does not disclose the limitations at issue, and further that the claimed limitations differ in scope from the original disclosure. The arguments are not persuasive because whether or not the enlargement of claim scope would be considered “substantial” or not, the amendments do undoubtedly go beyond the scope of the original disclosure, and therefore represent new matter.

43. With respect to the rejections of claims 1-3, 5, and 9-19 under 35 USC 112, 2<sup>nd</sup> paragraph, Applicant argues (see page 8) that the amendments have rendered the rejections moot. However, it is maintained for reasons of record that the use of the broad recitation “alkaline” together in the same claim (claim 1) with the narrower statement of the range “a pH...of about 10.5 to about 12.5” renders the claim indefinite (see above and the previous Office action at pages 9-10, item 19).

44. With respect to the rejections of claims 15-19 under 35 USC 103(a) as being obvious over Schmid in view of Vaynberg, Lou et al., and Serra et al., it is noted that the rejection has been withdrawn in favor of the above rejection of claims 15-20 over Schmid, Amiral, Vaynberg, and Lou. However, Applicant’s arguments (see pages 18-21) will be addressed insofar as they are relevant to the instant rejection. The arguments have been fully considered but they are not persuasive.

Applicant argues that the claims have been amended to recite that the claimed process excludes heat treatments or UV irradiation, and that Schmid teaches crosslinking (page 18). In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., exclusion of heat treatments or UV irradiation) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is noted that the claims recite that the method is performed "**in the absence of a crosslinking agent**" but do not specify exclusion of **heat treatments** or **UV irradiation**, as performed in the method of Schmid. As such, the arguments that the claimed process excludes heat treatments or UV irradiation are not persuasive since such limitations are not actually claimed.

In particular, the instant specification does not define what would be considered "crosslinking agents" according to the invention (this term does not appear in the specification). However, one skilled in the art would normally understand the term "agent" to refer to a chemical compound, rather than to a physical process such as heating or light irradiation. In the absence of a specific definition to indicate that heating or UV light would be encompassed by the term "crosslinking agents", this term may be reasonably construed as referring, for example, only to chemical compounds. Thus, the argument that Schmid teaches UV irradiation and heat treatment is not persuasive since the claims do not positively exclude such steps.

In response to applicant's arguments against the references individually (see page 19), one cannot show nonobviousness by attacking references individually where the rejections are

based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant further argues that although the references suggest that altering pH, salt, and incubation times may affect adsorption, the references fail to provide specific guidance as to what combination of features will produce the stable constructs of the present invention (page 19). This is not found persuasive because generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

It is incumbent upon Applicant to show that the particular range(s) is critical, generally by showing that the claimed range(s) achieves unexpected results relative to the prior art range. See MPEP 2144.05.

Applicant also alleges absence of guidance suggesting which specific parameters to modify (page 19), which is not persuasive since the parameters at issue (pH, incubation time, and ionic strength) are all specifically taught in the prior art as experimental parameters to optimize when adsorbing proteins onto polystyrene, as discussed in the rejection.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning (see page 20), it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the

time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant further argues that the Examiner has failed to explain how swelling of the polymer layer upon increased pH affects adsorption or bleeding rates of the formed product (pages 20-21). This argument is not persuasive for reasons of record (see the previous Office action at page 33, the last paragraph):

[I]t is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. There is no requirement that the prior art provide the same reason as the applicant to make the claimed invention. MPEP 2144.

### ***Conclusion***

45. Claims 1-3, 5, 9, 11-13, and 15-20 are rejected.
46. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Will et al. ("Dynamic Viscosity Measurements by Photon Correlation Spectroscopy" *International Journal of Thermophysics*, Vol. 16 (1995), pages 433-434) provides evidence that "photon correlation spectroscopy" as disclosed in the instant application is synonymous for "dynamic light scattering" (see page 434, first paragraph).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Christine Foster, Ph.D.  
Patent Examiner  
Art Unit 1641



LONG V. LE 04/27/08  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600